Design and validation of the first cell-impermeant melatonin receptor agonist

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Résumé en anglais	Background and Purpose The paradigm that GPCRs are able to prolong or initiate cellular signalling through intracellular receptors recently emerged. Melatonin binds to G protein-coupled MT1 and MT2 receptors. In contrast to most other hormones targeting GPCRs, melatonin and its synthetic analogues are amphiphilic molecules easily penetrating into cells, but the existence of intracellular receptors is still unclear mainly due to a lack of appropriate tools. Experimental Approach We therefore designed and synthesized a series of hydrophilic melatonin receptor ligands coupled to the Cy3 cyanin fluorophore to reliably monitor its inability to penetrate cells. Two compounds, one lipophilic and one hydrophilic, were then functionally characterized in terms of their affinity for human and murine melatonin receptors expressed in HEK293 cells and their signalling efficacy. Key Results Among the different ligands, ICOA-13 showed the desired properties as it was cell-impermeant and bound to human and mouse MT1 and MT2 receptors. ICOA-13 showed differential activities on melatonin receptors ranging from partial to full agonistic properties for the Gi/cAMP and ERK pathway and β-arrestin 2 recruitment. Notably, ICOA-13 enabled us to discriminate between Gi/cAMP signalling of the MT1 receptor initiated at the cell surface and neuronal mitochondria. Conclusions and Implications We report here the first cell-impermeant melatonin receptor agonist, ICOA-13, which allows us to discriminate between signalling events initiated at the cell surface and intracellular compartments. Detection of mitochondrial MT1 receptors may have an important impact on the development of novel melatonin receptor ligands relevant for neurodegenerative diseases, such as Huntington disease.
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